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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/914,006	01/07/2002	Lothar Eggeling	PT 1.1678	7184
23416	7590	12/22/2004	EXAMINER	
CONNOLLY BOVE LODGE & HUTZ, LLP P O BOX 2207 WILMINGTON, DE 19899			FRONDA, CHRISTIAN L	
			ART UNIT	PAPER NUMBER
			1652	

DATE MAILED: 12/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/914,006

Applicant(s)

EGGELING ET AL.

Examiner

Christian L Fronda

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10 September 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 14-40 is/are pending in the application.
- 4a) Of the above claim(s) 30-40 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 14-29 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 07 January 2002 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
- 1) ☒ Certified copies of the priority documents have been received.
 - 2) ☐ Certified copies of the priority documents have been received in Application No. _____.
 - 3) ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>9/04, 10/04</u> . | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

1. Newly submitted claims 30-40 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

Claims 30-40 is directed toward a method for producing L-valine using a microorganism having an increase activity of ilvD as a result of any mutation of the endogenous gene encoding ilvD. These claims are unrelated and different from the claims 14-29 in that claims 14-29 recite and use a microorganism that is transformed with the wild-type ilvD gene and/or ilvBNC gene in a method for producing L-valine. The method of claims 18-29 and method of claims 30-40 are distinct both physically and functionally and require different process microorganism, steps, reagents, and parameters.

A search of all claims 14-40 in the patent literature and the non-patent literature cannot be made without serious burden because the inventions require separate searches that have different limits, boundaries, scope, and subject matter. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their divergent subject matter and classification, restriction for examination purposes is proper.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 30-40 are withdrawn from consideration as being directed to a non-elected inventions. See 37 CFR 1.142(b) and MPEP § 821.03.

2. Claims 14-29 are under consideration in this Office Action.

3. The rejection of claims 1-13 under 35 USC 101 has been withdrawn in view of applicants' cancellation of claims 1-13. Claims 14-29 meet the requirements of 35 USC 101 since the claims recite a microorganism transformed with a gene construct containing a nucleic acid encoding ilvD gene product dihydroxy acid dehydratase.

4. The rejection of claims 1-13 under 35 USC 112, second paragraph, for being indefinite and omitting essential method steps has been withdrawn in view of applicants' cancellation of claims 1-13 and amendments to claims 14-17. New claims 18-29 meet the requirements of 35 USC 112, second paragraph, since the claims recite the steps of culturing a transformed microorganism whereby L-valine is produced.

5. The rejection of claims 14, 16, and 17 under 35 U.S.C. 102(b) as being anticipated by Reuter (reference of record) has been withdrawn in view of applicants' Exhibit A which is a

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letter showing that the reference was not published prior to February 26, 1999, where the instant application claims foreign priority from German application DE 199 07 576.0 filed February 26, 1999.

6. The rejection of claims 1, 4, 6, and 7-9 under 35 U.S.C. 102(b) as being anticipated by Inui et al. (JP 08089249 A2) is moot in view of applicants' cancellation of the claims and has been withdrawn. New claims 18-29 are not anticipated by the Inui et al. reference since the claims recite transformation of a microorganism with both a nucleotide sequence encoding ilvD and a nucleotide sequence encoding ilvBNC.

7. The rejection of claims 4, 6, and 7-9 under 35 U.S.C. 102(b) as being anticipated by Sato et al. (EP 356739) is moot in view of applicants' cancellation of the claims and has been withdrawn. New claims 18-29 are not anticipated by the Sato et al. reference since the claims recite transformation of a microorganism with both a nucleotide sequence encoding ilvD and a nucleotide sequence encoding ilvBNC.

Claim Rejections - 35 U.S.C. § 112, 1st Paragraph

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 14-29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are a genus claim that encompasses any microorganism transformed with any ilvD and/or ilvBNC genes from any biological source having any nucleotide sequence and structure. The scope of this genus includes many of the respective genes with widely differing structural, chemical, and physical characteristics from many biological sources. Furthermore, the genus is highly variable because a significant number of structural differences between genus members is permitted.

The specification provides a written description for a dihydroxy acid dehydratase of SEQ ID NO: 2 encoded by SEQ ID NO: 1, ketopantoate hydroxymethyl transferase of SEQ ID NO: 4

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encoded by SEQ ID NO: 3, and pantothenate ligase of SEQ ID NO: 5 encoded by SEQ ID NO: 3 from *Corynebacterium glutamicum*. However, neither the specification nor the general knowledge of those skilled in the art provide evidence of any description of a nucleotide sequence and structure which would be expected to be common to the members of the genus of *ilvD* and/or *ilvBNC* genes that would distinguish members of the genus from other genes. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed.

Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosed dihydroxy acid dehydratase of SEQ ID NO: 2, ketopantoate hydroxymethyl transferase of SEQ ID NO: 4, and pantothenate ligase of SEQ ID NO: 5 from *Corynebacterium glutamicum* alone is insufficient to describe the genus. Thus, one of skill in the art would conclude that Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed genus of *ilvD* and/or *ilvBNC* genes from any biological source having any nucleotide sequence and structure.

A review of the specification indicates that elements which are not particularly described, including regulatory elements and untranslated regions, are essential to the function of the claimed invention because the definition of "gene" known by those skilled in the relevant art requires them. The art indicates that the structure of genes with regulatory elements and untranslated regions is empirically determined. For example, the structural elements of "gene" mediating the expression of a particular protein in the liver may be different than the structural elements of the "gene" mediating the expression of the same protein in the brain. Therefore, the structure of these elements which applicants considers as being essential to the function of the claim are not conventional in the art.

There is no known or disclosed correlation between the disclosed nucleotide sequences of SEQ ID NO:1 and SEQ ID NO: 3 and the structure of the non-described regulatory elements and untranslated regions of the claimed genus of genes. Furthermore, there is no additional disclosure of physical and/or chemical properties. Thus, one of skill in the art would not recognize that applicants were in possession of the genus of genes from any biological source having any nucleotide sequence and structure, where the specification does not provide a written description of regulatory elements and untranslated regions that are essential to the function of each of the recited genes.

10. Claims 14-18, 20-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated microorganism transformed with a gene construct containing SEQ ID NO: 1 and SEQ ID NO:2, and a method for producing L-valine

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using said isolated microorganism; does not reasonably provide enablement for any other embodiment.

The nature and breadth of the claims encompass any microorganism transformed with any gene construct containing any ilvD and/or ilvBNC gene of any nucleotide sequence from any biological source, and a method for producing L-valine using said microorganism.

The specification discloses a dihydroxy acid dehydratase of SEQ ID NO: 2 encoded by SEQ ID NO: 1, ketopantoate hydroxymethyl transferase of SEQ ID NO: 4 encoded by SEQ ID NO: 3, and pantothenate ligase of SEQ ID NO: 5 encoded by SEQ ID NO: 3 from *Corynebacterium glutamicum*.

In order to meet the enablement requirement, one skilled in the art must be able to make the claimed invention without undue experimentation using the specification coupled with information known in the art. However, neither the specification nor the general knowledge of those skilled in the art provide guidance or prediction on making, without undue experimentation, any microorganism transformed with any gene construct containing any ilvD and/or ilvBNC gene of any nucleotide sequence from any biological source.

The amount of experimentation to make the claimed microorganism is enormous and undue. Such experimentation entails screening, searching, and isolating from any biological source any ilvD and/or ilvBNC gene of any nucleotide sequence, transforming the genes into any microorganism, where the activity of any ilvA, panB, panC, panE, and panD enzymes is reduced or eliminated, and determining whether the microorganism can still produce L-valine. In addition, such undue experimentation entails searching and screening for any type of deletion of any genes encoding ilvA, panB, panC, panE, and panD enzymes that will result in no synthesis of D-pantothenate in any microorganism. Teachings regarding screening and searching for any ilvD, ilvBNC, ilvA, panB, panC, panE, and panD genes of any nucleotide sequence from any biological source is not guidance for making the claimed invention.

It is well known in the prior art that organisms have specific codon preferences and that eukaryotic genes and polynucleotides often do not express in prokaryotic host cells because prokaryotic host cells recognize only specific codons which may not be used in eukaryotic genes and polynucleotides (see Zhou et al. Protein Expr Purif. 2004 Mar;34(1):87-94; entire publication, especially p. 87, right column, 1st full paragraph to p. 88, left column, 1st full paragraph). Thus, it cannot be predicted whether or not any ilvD or ilvBNC gene of from any biological source and nucleotide sequence can be functionally expressed in any microorganism and still produce L-valine in order to meet the limitations of the invention.

The Examiner finds that one skilled in the art would require additional guidance, such as information regarding the specific nucleotide sequence of and biological source of the ilvD or ilvBNC gene. Without such a guidance, the experimentation left to those skilled in the art is undue.

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Conclusion

11. No claims are allowed.

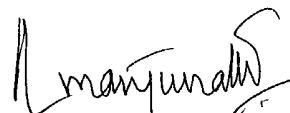
12. Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christian L Fronda whose telephone number is (571)272-0929. The examiner can normally be reached Monday-Friday between 9:00AM - 5:00PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura N Achutamurthy can be reached on (571)272-0928. The fax phone number for the organization where this application or proceeding is assigned is (571)273-8300.

14. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Christian L Fronda
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Majunath Rao
Primary Patent Examiner
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